Remarks

Applicants respectfully request that this application be reconsidered in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 1-11, 15-17, 20-26, and 28-34 are pending in this application of which Claim 15-17 and 28-34 are withdrawn from consideration. Applicants respectfully call the Examiner's attention to the cancellation of Claims 12-14, 18, 19, and 35-37 in their previous response dated October 2, 2006. No claims have been canceled or amended in this response. Accordingly, Claims 1-11, 15-17, 20-26, and 28-34 remain pending in this application.

2. Rejection of Claims 1-11 and 20-26 under 35 U.S.C. §103(a)

Claims 1-11 and 20-26 were again rejected under 35 U.S.C. §103(a) as being unpatentable over Moran et al. (US 6,576,793 B1). Applicants respectfully traverse these rejections for the reasons of record and for the following reasons.

Claims 1-11

Claims 1-7 are directed to a crystalline compound and Claims 8-11 are directed to pharmaceutical compositions comprising the crystalline compound. In particular, Claim 1 recites "crystalline *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride". The claim recites three distinct elements: the particular chemical compound (hereinafter compound 1), a particular salt of the compound, namely the dihydrochloride salt , and that the dihydrochloride salt of the compound be crystalline.

As required by M.P.E.P. §2143, to establish a *prima facie* case of obviousness, the Examiner must at least show (1) that the prior art reference teaches or suggests all the claim limitations, (2) that there is some suggestion or motivation, either in the reference or in the knowledge available to one of ordinary skill in the art, to modify the reference, and (3) that there is a reasonable expectation of success. Applicants continue to traverse

rejection because the Examiner has failed to meet the requirements for a *prima facie* showing of obviousness.

In the pending Office Action, the Examiner has taken the position:

> Inasmuch as the acid salts of the compounds are made, its physical characteristics is inherent and just because the reference has not mentioned the characteristic of the salt, does not preclude it to be crystalline as it is inherent to the nature of the salt. (Page 2, lines 9-12).

The rejection is based on incorrect premises

Applicants respectfully submit the Examiner's attempt to show the reference teaches the claim limitations is based on two incorrect premises. First he has posited that the reference discloses the dihydrochloride salt of compound 1: "inasmuch as the acid salts of the compounds are made", and second, he has presumed that such a salt is inherently crystalline: "it is inherent to the nature of the salt". Applicants respectfully submit that both of these assumptions are incorrect.

The reference does not disclose the dihydrochloride salt of the compound

The reference discloses *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)-phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine only as entry 10E in Table E, column 28. The synthesis of a racemic form of the compound is described in Example 12, columns 129-130. In neither of these locations is there any mention of any salt form. In particular, therefore, there is no disclosure of a dihydrochloride salt.

The only mention of salt forms in the reference is a list of pharmaceutically-acceptable base addition salts (col 19, lines 4-42), and acid-addition salts (col 19, lines 43-53) uncoupled from any discussion of any particular compound. Such a list is merely a disclosure of possible salts that might be prepared for any of the many compounds disclosed in the reference. The mere disclosure of a list of possible salts in a reference disclosing many compounds is not a specific disclosure of each salt of each compound. Therefore, since the reference does not disclose the dihydrochloride salt of the compound, it is erroneous to contend that "the acid salts of the compounds are made".

Inherency cannot be invoked

The Office Action argues that the present salt form is inherently crystalline. Such an argument regarding an inherent property of a compound would only be appropriate if the cited reference actually disclosed the dihydrochloride salt of the compound, but failed

to specifically recite that the salt was crystalline. However, as discussed above, the cited reference does not disclose any hydrochloride salt of compound **1**, let alone the dihydrochloride salt.

It is well established that a physical property of a compound cannot be inherently taught by a reference if the compound itself is not taught by the reference. Therefore, it is not proper to invoke inherency in this matter since the reference does not disclose the presently claimed dihydrochloride salt of compound **1**.

Furthermore, the requirements of an inherent rejection are not satisfied in the present instance. The case law relating to inherency is discussed extensively in MPEP §2112 (IV):

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534. 28 UPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis in original)
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> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily*** present ***in the thing described in the reference***, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)(citations omitted, emphasis added)
>
> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). (emphasis in original).

Applying these teachings to the present instance, even ***if*** the reference had disclosed the dihydrochloride salt of compound **1**, it would still only be proper to invoke inherency ***if*** that salt is ***necessarily*** crystalline. The ***possibility*** that the salt can be prepared in crystalline form is insufficient to support a rejection.

It is well established in the pharmaceutical arts that the formation of crystalline salts is unpredictable. See, for example, *Handbook of Pharmaceutical Salts*, P. H. Stahl, C. G. Wermuth, Eds., Verlag, Helvetica Chimica Acta, Zurich (2002), p. 137, 6th paragraph) ("No predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature."). Furthermore, the solid phase of a pharmaceutical salt can be amorphous or crystalline (see *ibid* pp 42-43); *see also Sanofi-Synthelabo v. Apotex, Inc.*, No. 02 Civ. 2255(SHS),

2006 WL 2516486, at *17 (S.D.N.Y. Aug. 31, 2006) ("[t]he evidence shows that salt formation is an unpredictable exercise, and that a chemist would not know, before testing various acids and bases, which one would cause a specific compound to crystallize and have pharmaceutically acceptable properties.")), *aff'd*, No. 06-1613, 2006 WL 3613616 (Fed. Cir. Dec. 8, 2006). Indeed, it is impossible to predict which particular acid will cause a particular base to crystallize into a salt. *See Pfizer*, 405 F. Supp. 2d at 517 ("Given the unique properties each salt imparts to the parent compound, salt selection is not a routine process and the success of a given salt is not easily predicted.").

The Examiner has not cited any extrinsic evidence to suggest why, in view of the unpredictability of salt formation, in general, and crystalline salt formation, in particular, a person skilled in the art would recognize that the specific dihydrochloride salt of compound **1**, were it to be formed, would necessarily be crystalline.

In an attempt to remedy the lack of extrinsic evidence, the Examiner has put forward a technical argument in support of his assertion that a dihydrochloride salt of compound **1** is inherently crystalline, i.e. cannot be amorphous:

> However, in the instant compound, there are no basic functional radicals which will overtake the acid part to form the amorphous natured compound. In the instant compound, it is a simple compound with no basic or acidic group present and its acid salt is likely to give crystalline form of the compound. (Page 2, lines 13-17).

Although, according to MPEP §2144.02, an examiner may rely on logic and sound scientific principles in support of a rejection under § 103 (*see In re Soli*, 317 F.2d 941, 947, 127 USPQ 797 (CCPA 1963)), the examiner must provide some evidentiary basis for the existence and meaning of the scientific principle relied on. *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979).

In the present instance, the Examiner has not provided any authority to support his theory with respect to the existence or nonexistence of amorphous solids. Furthermore, the technical argument is incorrect with respect to the present compound. If there were actually "no basic groups present" in the subject compound, it would not be possible to form an acid salt. The Examiner, himself noted the presence of two nitrogen atoms capable of participating in acid salt formation, which contradicts his assertion that no basic groups are present in the compound. Applicants respectfully submit the Examiner's theory cannot be given any weight.

In summary, Applicants have demonstrated: (1) the reference does not disclose the dihydrochloride salt of compound **1**, and (2) the Examiner has failed to establish that a dihydrochloride salt of compound 1 is inherently crystalline. For these reasons and the reasons of record, the Examiner has not established a *prima facie* case of obviousness. Therefore, the rejection of Claim 1 and claims dependent therefrom is improper and should be withdrawn.

In particular, Claims 2-7 recite specific characteristics of the crystalline dihydrochloride salt of Claim 1. Since the Office Action has failed to establish that the present salt form is ***necessarily*** crystalline, it certainly has failed to establish that the salt of compound **1** would ***necessarily*** have the specific x-ray powder diffraction pattern recited in Claims 2-4 and 7, the infrared absorption spectrum of Claim 5, and the differential scanning calorimetry characteristic of Claim 6. For these additional reasons as well, Claims 2-7 are patentable over Moran '793.

Rejection of Claims 20-26

Claims 20-26 recite a pharmaceutical composition comprising *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride; a buffering agent; and water; wherein the buffering agent is present in an amount sufficient to provide the composition with a pH in the range of between about 4 and about 6. The Office Actions in this application have failed to address the specific subject matter of Claims 20-26. Similarly, they have failed to consider Applicants' responses with respect to these claims.

Moran '793 does not teach or suggest a pharmaceutical composition with the limitations of Claim 20 and claims dependent therefrom. The Examiner has failed to establish a *prima facie* case of obviousness for Claims 20-26 based on Moran '793.

Furthermore, at page 9, lines 9-16, the specification provides objective evidence of the unexpected benefits of a pharmaceutical composition according to Claims 20-26, namely evidence of the stability of the pharmaceutical composition of Claims 20-26 upon storage. In contrast, U.S. 6,040,344 identified stability of a pharmaceutical composition of formoterol tartrate, a different β_2 adrenergic receptor agonist, prepared for the same form of administration, as a limitation to its acceptability. Consideration of the present evidence of unexpected results, further supports the patentability of Claims 20-26.

In summary, Claims 1-11 and 20-26 have been shown to be patentable over Moran '793. Accordingly, the present rejection of Claims 1-11 and 20-26 under 35 U.S.C. §103(a) should be withdrawn.

4. Provisional Double Patenting Rejection

Claims 1-11 and 20-26 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-28 of copending application no. 10/854,405. Applicants submit herewith a terminal disclaimer in compliance with 37 C.F.R. §1.321(c). Accordingly, this rejection may be withdrawn.

Additionally, for the sake of completeness, Applicants wish to bring to the Examiner's attention copending application no. 11/654,117 listed as reference A1 on the Form PTO/SB/08a filed herewith. In order to expedite the prosecution of the present application to allowance, Applicants are submitting a terminal disclaimer in compliance with 37 C.F.R. §1.321(c) to obviate a rejection of the present claims over 11/654,117 in the event that the Examiner determines that the '117 application raises an obviousness-type double patenting rejection. Applicants respectfully request that the Examiner indicate on the record in the next paper on the merits whether this second terminal disclaimer has been entered.

Applicants note that the filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). Specifically, the courts have indicated that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection."

5. Conclusion

In view of the foregoing, Applicants respectfully submit Claims 1-11 and 20-26 are in condition for allowance. Further, upon allowance, according to *In re Ochiai* (71F. 3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and MPEP §821.04, the restriction between Group I and Groups III (pending Claims 15-17) and V (Claims 28-30), both of which are process claims, and between Group I and Group VI (pending Claims 31-34), which are method of use claims, may be withdrawn. Reconsideration of this application and prompt passage to allowance is respectfully requested. Should there be any issues regarding this application that may be resolved by telephone, the examiner is invited to telephone the undersigned agent for Applicants at (650) 808-3764 (direct).

Respectfully submitted,
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